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Redox control of tumor cell apoptosis during hypoxia

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Abstract

Currently, close attention is paid to studies aimed at searching for redox-sensitive targets for the regulation of tumor cell death. Tumor growth is characterized by impaired cell proliferation, differentiation, and apoptosis against the background of oxidative stress. Hypoxia contributes to the formation of mitochondrial dysfunction and acts as an additional factor that exacerbates oxidative stress in the tumor cell. Reactive oxygen species are general damaging factors, however, they can act as modulators of processes such as reception, intracellular signaling, proliferation, apoptosis, while taking part in the functioning of the cell redox system and contributing to the oxidative modification of macromolecules. One of the possible reasons for the activation of the production of reactive oxygen species is the low content of O_2 in the cell, the final electron acceptor to ensure the functioning of the enzymes of the mitochondrial respiratory chain. The glutathione system makes a significant contribution to maintaining the balance between prooxidants and antioxidants in the cell. The role of this system is justified by the reduction potential of glutathione, which, acting as an acceptor of hydroxyl ions and singlet oxygen, significantly reduces the cytotoxic and damaging effects of reactive oxygen species. At the same time, it serves as a coenzyme for glutathione-dependent enzymes, which play a leading role not only in providing antioxidant processes, but also in maintaining the thiol disulfide balance. Hypoxia, which acts as a factor in the activation of free radical oxidation against the background of proliferation and apoptosis dysregulation, contributes to the formation of resistance of tumor cells to chemotherapeutic effects. In light of this, the importance of studying the redox-dependent mechanisms involved in the regulation and implementation of tumor cell death under insufficient oxygen supply becomes obvious, which is necessary for the development of personalized antitumor therapy. The article presents a review of modern literature, including the results of our own research, on the role of the thiol disulfide system and oxidatively modified proteins in the redox regulation of proliferation and apoptotic death of tumor cells, including under hypoxic conditions.

Keywords: tumor cells, apoptosis, hypoxia, oxidative stress, glutathione system, redox-status.

Abbreviations: ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; EPR, endoplasmic reticulum; FIH, factor inhibiting hypoxia-inducing factor-1; GSH (glutathione-SH), reduced glutathione; GSSG (glutathione-S-S-glutathione), oxidized glutathione; HIF, hypoxia-inducible factor; HRE, hypoxia-responsive element; PHD 1–3, prolyl hydroxylase domain proteins; ROS, reactive oxygen species.

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Background

Currently, the study of molecular mechanisms of malignancy and survival of tumor cells is relevant. Apoptosis is genetically determined and underlies vital processes, such as embryogenesis, cell and tissue renewal, and aging. The dysregulation of the process of programmed cell death is one of the major factors in the development of many human diseases, such as oncological, neurodegenerative, and autoimmune diseases [1–3]. Thus, the study of the molecular mechanisms of apoptotic death and functioning of signaling pathways that control cell cycle phases and apoptosis is important in both theoretical and practical medicine.

Tumor growth, hypoxia, and oxidative stress

Tumor growth is characterized by uncontrolled rates of deoxyribonucleic acid (DNA) replication, impaired cell differentiation, apoptosis, oxidative stress, and metabolic changes [4–6]. Replication requires increased synthesis of macroergs, which depends directly on oxygen tension in cells. Mitochondria and endoplasmic reticulum (EPR) are leading organelles that meet the requirements for the synthesis of adenosine triphosphate (ATP) and proteins of a malignant cell to implement high rates of division and growth [7].

The relationship between EPR and mitochondria is mediated by the maintenance of intracellular

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homeostasis of Ca^{2+} ions, which affect the implementation and regulation of programmed cell death [8]. With uncontrolled growth, a clone of tumor cells may be deprived of adequate oxygen supply for some time because of insufficient angiogenesis; therefore, hypoxia develops in malignant cells, leading to the disruption of the functioning of the mitochondrial respiratory chain and increased production of reactive oxygen species (ROS) [8, 9].

Under these conditions, ATP synthesis in tumor cells results from the glycolytic oxidation of glucose. ROS participation in redox signaling determines the leading role of mitochondria in the transformation of normal cells into malignant ones [10]. According to Chen et al., tumor growth depends on the intracellular level of ROS. A low intracellular ROS concentration promotes the proliferation of malignant cells and cancer invasion, whereas excessive amounts of ROS in tumor cells have cytotoxic effects [11–13].

Characteristics of the metabolism of tumor cells during hypoxia

Hypoxia and oxidative stress underlie the development of pathological processes, including tumor growth [14–16]. To date, in response to an insufficient oxygen supply to cells and the activation of free radical oxidation, apoptosis, and other types of cell death (e.g., ferroptosis, necrosis, and autophagy) can be triggered [17]. Low oxygen tension contributes to the disruption of apoptosis of tumor cells and the appearance of additional resistance to therapeutic effects [18]. The molecular mechanism underlying these changes is the activation of transcription of genes encoding information about proteins, including glycolysis enzymes and transcription factors, namely, hypoxia-inducible factors (HIFs), nuclear factor-κB, Apaf-1, and others [11, 19, 20].

Hypoxia occurs under conditions of intracellular oxygen tension of 1%–5%, and the complete absence of oxygen (in practice, <0.02%) is commonly called anoxia. The lack of oxygen supply can be acute (minutes to hours) or chronic (hours to days). Moreover, both hypoxia severity and duration are important factors that determine the cellular response to this effect [18]. Thus, the role of intracellular signaling in the dysregulation of apoptosis during hypoxia in both normal and tumor cells is important [15, 16, 21].

In response to hypoxia in the cell, transcription factors with a wide spectrum of action, called HIFs, are activated. The HIF family includes three members, namely, HIF-1, HIF-2, and HIF-3. However, HIF-1 is believed to play the leading role in hypoxia. A common feature of all transcription factors of this group is their ability to bind to a specific DNA nucleotide sequence called hypoxia-responsive element (HRE), of more than 100 genes in the promoter region, whose expression is thus regulated by oxygen tension. All transcription factors of HIFs are heterodimers consisting of two parts, namely, an oxygen-sensitive HIFα subunit and a stable HIFβ subunit. The activity of the entire HIF complex is regulated by the α-subunit, which is rapidly destroyed under normoxic conditions, preventing dimerization [22].

In eukaryotic cells, the sensors of low partial pressure of oxygen in the environment, namely, enzymes of the electron transport chain in the inner membrane of mitochondria, members of the prolyl hydroxylase family [prolyl hydroxylase domain (PHD 1–3) proteins], and factor inhibiting HIF-1 (FIH), have been studied comprehensively. The production of ROS under hypoxic conditions is increased because of the loss of electrons in complexes I and III of the electron transport chain of the inner mitochondrial membrane [23, 24]. Thus, by producing ROS and serving as a depot of Ca^{2+} ions, mitochondria under hypoxic conditions are the most significant in triggering and regulating signaling cascades [5, 11, 25].

The activity of prolyl hydroxylases of the transcription factor HIF can be inhibited with increased ROS concentration, which is due to the oxidation of the iron ion, which is part of the active sites of enzymes. Moreover, several antioxidants, including N-acetylcysteine, can interfere with ROS-induced stabilization of HIF-1α [26]. FIH and/or prolyl hydroxylases may be also involved in the occurrence of metabolic disorders in tumor cells with decreased oxygen tension because these enzymes require molecular oxygen for the hydroxylation of proline amino acid residues in HIF. Thus, FIH and PHD are sensitive to oxygen content and necessary for optimal stabilization and activation of HIF-1α [22].

Under normoxic conditions, PHD hydroxylates HIF-1α at certain proline residues in the domain responsible for oxygen-dependent degradation. Hydroxylated HIF-1α residues are recognized by E3 ubiquitin ligase for ubiquitinylation and further degradation by proteasomes [27, 28]. Under hypoxic conditions, hydroxylation is limited; therefore, HIF-1α can move into the nucleus, dimerize with HIF-1β, bind to HRE, and activate gene transcription.

Much later, studies have revealed the ability of FIH to hydroxylate aspartic residues in the C-terminal activation domain of HIF-1α and thus inhibit the transcriptional activity of the factor. The activity of both PHD and FIH depends on oxygen concentration; however, oxygen tension >5% is required for FIH inactivation [29].

Consequently, some genes, whose expression is regulated by hypoxia, are activated at different oxygen pressures in cells. This explains the different cellular responses at varying levels of hypoxia. For example, the maximum expression of vascular endothelial growth factor occurs at 2% intracellular O_2 level, whereas the maximum expression of HIF-1α occurs at 1% O_2 tension [30].

The involvement of HIF-1 in gene expression regulation is mainly represented by three basic strategies aimed at maintaining cell activity under adverse conditions, namely, the activation of glycolysis, ATP synthesis, and angiogenesis. Target genes include genes that encode vascular endothelial growth factor, erythropoietin, insulin-like growth factor 2, transforming growth factor α, glucose transporter-1, and glycolysis enzymes [31, 32]. The activation of the transcription of these genes is usually noted under mild hypoxia. However, severe and chronic hypoxia associated with ROS accumulation leads to HIF-1-dependent activation of genes involved in cell death (genes encoding the p53 protein, caspase 3, etc.) [33].

Under hypoxic conditions, transcription factors of the HIF family are considered the main regulators of the cellular response by changing the activity of the mammalian target of rapamycin kinase and components of the unfolded protein response signaling cascade. In addition, under hypoxic conditions, EPR functioning changes, which are associated with impaired protein folding, leading to cell death initiation. The glucose-regulated chaperone GRP 78 plays the most important role in triggering the signaling cascade [34].

Under hypoxic conditions, tumor cells can induce HIF-1-mediated factors, such as insulin-like growth factor 2, which promotes cell survival; glucose transporter-1, which increases glucose uptake; vascular endothelial growth factor, which stimulates angiogenesis; hepatocyte growth factor receptor (c-Met), which increases the ability to invade; and receptor 4 for CXC chemokines, which increases the ability to metastasize [35]. Certain authors claim that resistance to therapy, metastatic spread, and deterioration in the overall prognosis of cancer correlate directly with hypoxia formation in tumor cells [18, 36].

In one tumor, several types of cells with different levels of oxygen tension can be present simultaneously because vascular blood flow can vary in different parts of the tumor [18]. Changes in cell metabolism in response to hypoxia stimulate angiogenesis and genome transcriptional activity, which promote the transformation of normal cells into malignant ones [36]. In addition, hypoxia during tumor progression triggers certain mutations in genes that regulate cell proliferation, such as the genes for the p53 protein and epidermal growth factor receptor, thereby promoting the malignancy of tumor cells [37].

The occurrence of apoptosis depends on the intracellular concentration of Ca^{2+} ions, which is regulated by ion-transporting systems. Data indicated that even small shifts in calcium levels in the cell can lead to adverse effects, such as disruption of proliferation and apoptosis [38]. Ca^{2+} ions enter the cell through the cytoplasmic membrane mainly due to ligand-dependent and voltage-dependent calcium channels [39].

In the cytoplasm, Ca^{2+} ions either interact with calcium-binding proteins or enter the EPR and mitochondria or are removed into the intercellular space by Ca^{2+}-ATPase and Na^{+}/Ca^{2+}-exchanger located on the plasmalemma. The levels of Ca^{2+} ions in the EPR depend on the work of Ca^{2+}-ATPase and receptors for inositol-1,4,5-triphosphate and rhyanodine receptors. In addition, this indicator depends on the activity of calcium-binding proteins (calreticulin and calsequestrin) in the EPR. Ca^{2+} ions enter the mitochondria through the uniport, and they can be released in different ways, namely, by reversing the uniport, because of the operation of the Na+/H+-dependent Ca^{2+} exchanger or as a result of the opening of mitochondrial pores [40]. Impaired intracellular homeostasis of Ca^{2+} ions is a characteristic sign of apoptosis. In this case, Ca^{2+} ion concentration in the cytoplasm increases significantly because of increased entry into the cell and release from the EPR and mitochondria [41].

Thus, a reduced intracellular oxygen level leads inevitably to disrupted functioning of mitochondria, development of oxidative stress, and change in the content of Ca^{2+} ions. Under enhanced proliferation and impaired cell differentiation against oxidative stress, regulation disorders and apoptosis of tumor cells occur. Thus, studies of the molecular mechanisms of the regulation of intracellular signal transduction for the occurrence of apoptosis under oxidative stress that accompanies hypoxia development remain relevant and will expand the existing fundamental ideas about the mechanisms of maintaining the redox balance of cells and control the functional activity of ion-transporting systems during hypoxia in tumor cells.

Redox regulation in tumor cells

In molecular biology, ROS are not only cytotoxic agents but also, under certain conditions, function as signal molecules for the redox regulation of cellular functions [13, 42, 43]. The sensitivity of redox-dependent signaling pathways is attributed to the oxidative modification of macromolecules that

serve as intracellular sensors for changes in the redox balance [44]. Thus, the redox control of the activity of key components of signaling pathways, transcription factors, and apoptosis by glutathionylation must be examined [45–47].

Our studies on tumor cell lines helped us establish the relationship between changes in the redox status of the glutathione system, oxidative modification of proteins, and dysregulation of cell death and proliferation. Thus, the cultivation of MCF-7 cells in the presence of a protector of the SH groups of proteins and peptides (1,4-dithioerythritol) was found to result in a decrease in the proliferative activity of cells against a change in the redox state caused by low concentrations of cyclin E, CDK2, and CDK4 under the influence of glutaredoxin and glutathione systems and in a pronounced protective effect of the compound on the oxidative modification of proteins, such as decreased levels of carbonyl derivatives of proteins during spontaneous and metal-catalyzed oxidation, contents of bityrosine and oxidized tryptophan compared with similar indicators in intact cells of the MCF-7 line) [6, 48].

Under hypoxic conditions, P19 tumor cells were characterized by increased ROS production and changes in the redox status of cells. Moreover, a direct relationship has been established among dysregulated calcium homeostasis, protein glutathionylation, depolarization of the inner mitochondrial membrane, and triggering of programmed death of tumor cells [15, 16, 49].

The use of a de novo glutathione synthesis inhibitor (buthionine sulfoximine) activated the programmed death of Jurkat tumor cells caused by increased formation of hydroxyl radicals and high concentrations of protein carbonyl derivatives against a decrease in the levels of protein-bound glutathione and oxidized tryptophan [50].

The main representatives of ROS include singlet oxygen $^1O_2$, superoxide anion radical $O_2^{\bullet -}$, hydroxyl radical $HO^{\bullet}$, peroxide radical $HOO^{\bullet}$, and, of course, hydrogen peroxide H_2O_2 [51, 52].

ROS that are constantly formed in cells are inactivated by the antioxidant system, which includes enzymatic and non-enzymatic units. The disruption of this system underlies the formation of oxidative stress, which is characterized by the accumulation of oxidatively modified macromolecules in cells [53, 54]. The main antioxidants include low-molecular-weight (vitamins E and C, glutathione, etc.) and high-molecular-weight (enzymes superoxide dismutase, catalase, and glutathione peroxidase) compounds [53, 55].

Glutathione [γ-L-glutamyl-L-cysteinylglycine, GSH (glutathione-SH, reduced glutathione)] is a tripeptide that contains a thiol group and is synthesized in the cytosol of cells in two stages using ATP.

At the initial stage, given the activity of γ-glutamylcysteine synthetase, γ-glutamylcysteine is formed from glutamate and cysteine, after which glutathione synthetase uses this product and glycine as substrates for glutathione synthesis. Owing to the presence of a cysteine residue in glutathione composition, this peptide plays an important role in the regulation of the state of disulfide bonds in proteins and levels of prooxidants in cells [56–58]. The importance of glutathione as an intracellular redox buffer is confirmed by its low redox potential (E_0' = –240 mV), high concentrations in cells, and involvement in various cellular reactions, such as intracellular signal transduction, xenobiotic metabolism, regulation of proliferation, and apoptosis [47, 54–56, 59].

Although glutathione is synthesized exclusively in the cytosol, it is present in many organelles, including the EPR, mitochondria, and nucleus [57, 60]. Glutathione distributed over cell compartments forms independent redox pools with different redox potentials [61]. In the nucleus, glutathione maintains the functionally active state of proteins by glutathionylation of sulfhydryl groups, which is necessary for important processes such as DNA transcription and repair [57, 62]. In the EPR, the tripeptide is mainly in the oxidized form (GSSG, glutathione-S-S-glutathione, oxidized glutathione), which is involved in the formation of disulfide bonds during the folding of synthesized proteins [62]. The mitochondrial fraction of glutathione is approximately 10%–15% of its total content in cells and is represented mainly by the reduced form. Considering the amount of the mitochondrial matrix, the concentration of mitochondrial glutathione is similar to that of the cytosolic fraction, which amounts to 10–14 mM [62].

To date, ROS are confirmed to be involved in various signaling cascades, leading to different types of biological cell responses [13, 42, 43, 63]. Among ROS types, only H_2O_2 has all the characteristics required for secondary messengers; first, it is a low-molecular electrically neutral molecule that can diffuse and freely penetrate cell membranes. Second, H_2O_2 is rapidly generated in response to various stimuli and can be easily removed through certain mechanisms. Third, H_2O_2 can act on certain proteins containing thiol groups in active centers [64].

The dismutation reaction of the superoxide anion radical ($O2^{\bullet -}$) catalyzed by superoxide dismutase (EC (enzyme classification) 1.15.1.1) is the main source of H_2O_2 molecules in cells [65]. Further, the formed H_2O_2 can diffuse into the cytosol

or be involved in a sequence of reactions leading to the formation of other free radicals, for example, a hydroxyl radical that can oxidize biomacromolecules (proteins, lipids, and DNA) [66, 67].

Several important biomolecules, such as FAD2[1], FMN[2], and NAD[3], can spontaneously oxidize in the presence of O_2 to form $O_2^{\bullet-}$. However, in most cases, this does not lead to a significant increase in the level of $O_2^{\bullet-}$ in cells because it is mainly formed through one-electron reduction of O_2 in the electron transport chain in mitochondria [68]. Moreover, complex I of the respiratory chain generates $O_2^{\bullet-}$ predominantly into the mitochondrial matrix, whereas complex III generates $O_2^{\bullet-}$ on both sides of the inner mitochondrial membrane [69]. This process is influenced by several factors, including intracellular oxygen tension [70].

Most of the $O_2^{\bullet-}$ formed in the cells is converted into H_2O_2. However, $O_2^{\bullet-}$, which has avoided the degradation by the antioxidant defense system, reacts mainly with nitric oxide and metals with transitional valence, for example, with iron in the composition of the iron-sulfur centers of proteins [(2Fe-2S) centers in the composition of protein molecules]. Among Fe-S-containing proteins interacting with $O_2^{\bullet-}$, aconitase, ribonucleotide reductase, and guanylate cyclase can be noted [71].

H_2O_2 can participate in the reactions of reversible oxidative modification of thiol groups of proteins and thereby regulate their functions. As a signaling molecule, H_2O_2 can react directly with amino acid residues in protein molecules or exert influence through the GSH/GSSG pair [69]. In some cases, this leads to the inhibition of the activity of enzymes, for example, from the family of tyrosine phosphatases [72].

The rate of reaction of thiol groups with H_2O_2 is one of the main factors that determine the ability of proteins to interact with H_2O_2 and, consequently, participate in redox regulation. Cysteine thiolate anion provides greater bioavailability for interaction with H_2O_2 of cysteine residues in proteins. However, at physiological hydrogen ion concentration (pH) for most thiol groups in proteins, the pK_a value (equilibrium protein-SH ↔ protein-S^- + H^+) is 8.0–8.5; therefore, sulfur and hydrogen atoms are bonded. For this reason, if cysteine is located near positively charged amino acid residues, the pK_a value decreases to 5, which leads to the deprotonation of the SH group and oxidation with H_2O_2 to sulfenic acid (R-SOH) as protein-S^- + H_2O_2 → protein-SOH + HO^-. This molecular mechanism underlies the specific oxidative modification of cysteine residues in proteins, which is an integral part of redox signaling [73].

Some proteins can form sulfenates; however, owing to their low stability, they often undergo further modifications or reduction [74]. In the presence of H_2O_2, sulfenic acid can be oxidized to sulfinic and sulfonic acids (protein-SOH + H_2O_2 → protein-SO_2H + H_2O and protein-SO_2H + H_2O_2 → protein-SO_3H + H_2O).

Unlike sulfenic acid, sulfinic and sulfonic acids are stable and difficult to recover in vivo. The formation of sulfinic acids is significant in the redox regulation of the activity of proteins, particularly peroxiredoxins (oxidation of cysteine residues that are part of the active sites of enzymes, and the formation of sulfinic acids leads to their inhibition). Interestingly, sulfinic acids in the structure of peroxiredoxins can be slowly reduced to sulfenic acids because of the activity of sestrins in the reaction involving ATP. The formation of sulfonic acids is considered irreversible; at least, no mechanisms for their reduction in vivo have been revealed [75].

Sulfenic acids in proteins can react with thiol groups that are part of low-molecular-weight compounds or other proteins with the formation of disulfide bonds (protein-SOH + RS^- → protein-S-S-R + HO^-).

If the protein molecule comprises thiol groups, then intramolecular disulfide bonds are formed. However, if no free SH groups are present in the protein molecule for interaction, then the thiol groups of cysteine residues oxidized to sulfenates can form mixed disulfides with low-molecular compounds containing SH groups (e.g., with glutathione, cysteine, or coenzyme A) or with other proteins such as thioredoxin. Possibly, owing to the high concentration of glutathione in cells, protein glutathionylation is a common modification that can regulate the activity of certain proteins [76, 77].

In addition to the modification of cysteine residues, H_2O_2 can be involved in redox regulation through a shift in the ratio of reduced and oxidized forms of glutathione and thioredoxin in cells. Both are present in cells in high concentrations and are maintained in a reduced form by the activity of NADPH[4]-dependent reductases [78, 79]. Since these reactions can occur in vivo, the formation of disulfide bonds between two glutathione molecules and intramolecular disulfide bonds in thioredoxin resulting from the enzymatic destruction of H_2O_2 is a more probable mechanism for H_2O_2-dependent redox signaling.

H_2O_2 is utilized by the activity of catalase (EC 1.11.1.6), glutathione peroxidase (EC 1.11.1.9), and

[1] FAD, flavine adenine dinucleotide.

[2] FMN, flavine mononucleotide.

[3] NAD, nicotineamide-adenine dinucleotide.

[4] NADP, nicotineamide-adenine dinucleotide phosphate.

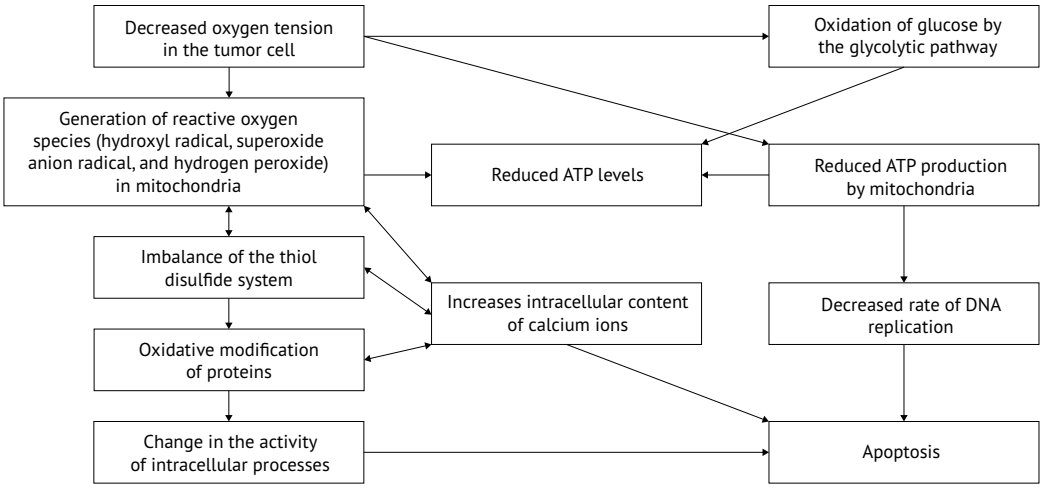

Fig. 1. Molecular mechanisms of the dysregulation and apoptosis in tumor cells during hypoxia; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid.

peroxiredoxin (EC 1.11.1.15) [80]. Consequently, the concentration of oxidized forms of glutathione and thioredoxin increases, which results in their interaction with key thiol groups in protein molecules because of thiol disulfide exchange reactions of protein-S^- + GSSG → protein-SSG + GS^-. These reactions proceed slowly in cells; however, glutaredoxin can accelerate these reactions [46, 81].

For participation in redox signaling, oxidative modification of proteins must be reversible and controlled. In most cases, H_2O_2-induced changes are reversible because of interaction with reduced pools of glutathione and thioredoxin. Thus, their redox state is an important factor that influences the post-translational modification of proteins. Since sulfinate reduction in the composition of proteins is an ATP-dependent process, this is associated with the energy state of the cells. Glutathione is also involved in the reduction of oxidized SH groups of proteins, and deglutathionylation reactions, such as glutathionylation, are catalyzed by glutaredoxins [46].

An intracellular increase in the levels of free radicals often leads to $O_2^{\bullet-}$ (as a result of $HOO^\bullet$ deprotonation) and H_2O_2 production. In the presence of metal ions of variable valence, two ROSs can interact with each other to form a hydroxyl radical ($O_2^{\bullet-} + H_2O_2 \rightarrow O_2 + HO^- + HO^\bullet$) [82].

The presence of a selenium atom in the active site of the amino acid residue L-selenocysteine is an important aspect of glutathione peroxidase [83]. Thioredoxin reductase (EC 1.8.1.9) is also a selenoprotein in mammals [84, 85]. Eight glutathione peroxidase isoforms encoded by different genes have been found in mammals [86]. All isoenzymes differ in their localization in the body and substrate specificity. Thus, glutathione peroxidase 1 is present in the cytoplasm and is responsible for H_2O_2 destruction in mammalian cells, whereas glutathione peroxidase 4 catalyzes the reduction of membrane lipid peroxides.

As noted above, unlike catalase, glutathione peroxidase requires GSH to reduce H_2O_2. This circumstance determines the important role of glutathione peroxidase as a redox sensor of the reduced levels of glutathione in cells. By participating in peroxide reduction, glutathione peroxidases are involved in cellular redox signaling. In addition, their activity increases the concentration of GSSG, which causes post-translational modification of proteins (glutathionylation) [87].

Oxidized glutathione is again reduced at the expense of $NADPH•H^+$ because of the activity of glutathione reductase (EC 1.8.1.7). In the enzyme's structure, the electrons move in the direction from $NADPH•H^+$ to FAD and further to disulfides, which in their reduced form can interact with GSSG by the covalent modification mechanism with GSSG + $NADPH•H^+ \rightarrow 2GSH + NADP^+$.

Peroxiredoxins reduce H_2O_2 at the expense of the SH groups of proteins, mainly thioredoxin, where H_2O_2 + thyroidoxin-$(SH)_2 \rightarrow 2H_2O$ + thioredoxin-(SS). The oxidized form of thioredoxin is reduced by thioredoxin reductase in the presence of $NADPH•H^+$. The active site of peroxiredoxins contains one or two cysteine residues.

The results of our studies and literature data are shown in Fig. 1.

Conclusion

Currently, studies aimed at searching for redox-sensitive targets for the regulation of tumor cell death received close attention. Impaired implementation and regulation of apoptosis occur during tumor

growth, which become important factors that determine the emergence and development of malignant neoplasms.

The targeted activation of apoptosis in tumor cells is one of the aims of current anticancer therapy [88]. Since the activation of free radical oxidation is an integral part of the pathogenesis of tumor growth and ROS can be directly involved in intracellular signaling, the glutathione system state modulation is considered one of the promising approaches for redox control of cell death in malignant cells [58].

Hypoxia, as a factor in the activation of free radical oxidation against the dysregulation of proliferation and apoptosis, contributes to the development of resistance to chemotherapeutic effects on tumor cells [18]. Thus, the mechanisms involved in the regulation and implementation of apoptosis of tumor cells with insufficient oxygen supply must be explored, which is necessary for the further formation of personalized antitumor therapy.

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